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Abstract: AIMS: Patients with chronic heart failure (CHF) show impaired health-related quality of life (HRQoL), an important target for therapeutic intervention. Impaired iron homeostasis may be one mechanism underlying the poor physical condition of CHF patients. This detailed subanalysis of the previously published FAIR-HF study evaluated baseline HRQoL in iron-deficient patients with CHF and the effect of intravenous ferric carboxymaltose (FCM) on HRQoL. **METHODS AND RESULTS:** FAIR-HF randomized 459 patients with reduced left ventricular ejection fraction and iron deficiency, with or without anaemia, to FCM or placebo (2:1). Health-related quality of life was assessed at baseline and after 4, 12, and 24 weeks of therapy using the generic EQ-5D questionnaire and disease-specific Kansas City cardiomyopathy questionnaire (KCCQ). Baseline mean visual analogue scale (VAS) score was 54.3 ± 16.4 and KCCQ overall summary score was 52.4 ± 18.8 . Ferric carboxymaltose significantly improved VAS and KCCQ (mean differences from baseline in KCCQ overall, clinical and total symptom scores, $P < 0.001$ vs. placebo) at all time points. At week 24, significant improvement vs. placebo was observed in four of the five EQ-5D dimensions: mobility ($P = 0.004$), self-care ($P < 0.001$), pain/discomfort ($P = 0.006$), anxiety/depression ($P = 0.012$), and usual activity ($P = 0.035$). Ferric carboxymaltose improved all KCCQ domain mean scores from Week 4 onward ($P \leq 0.05$), except for self-efficacy and social limitation. Effects were present in both anaemic and non-anaemic patients. **CONCLUSIONS:** HRQoL is impaired in iron-deficient patients with CHF. Intravenous FCM significantly improved HRQoL after 4 weeks, and throughout the remaining study period. The positive effects of FCM were independent of anaemia status.

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The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study

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Aims

Patients with chronic heart failure (CHF) show impaired health-related quality of life (HRQoL), an important target for therapeutic intervention. Impaired iron homeostasis may be one mechanism underlying the poor physical condition of CHF patients. This detailed subanalysis of the previously published FAIR-HF study evaluated baseline HRQoL in iron-deficient patients with CHF and the effect of intravenous ferric carboxymaltose (FCM) on HRQoL.

Methods and results

FAIR-HF randomized 459 patients with reduced left ventricular ejection fraction and iron deficiency, with or without anaemia, to FCM or placebo (2:1). Health-related quality of life was assessed at baseline and after 4, 12, and 24 weeks of therapy using the generic EQ-5D questionnaire and disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ). Baseline mean Visual Analogue Scale (VAS) score was 54.3 ± 16.4 and KCCQ overall summary score was 52.4 ± 18.8 . Ferric carboxymaltose significantly improved VAS and KCCQ (mean differences from baseline in KCCQ overall, clinical and total symptom scores, $P < 0.001$ vs. placebo) at all time points. At Week 24, significant improvement vs. placebo was observed in four of the five EQ-5D dimensions: mobility ($P = 0.004$), self-care ($P < 0.001$), pain/discomfort ($P = 0.006$), anxiety/depression ($P = 0.012$), and usual activity ($P = 0.035$). Ferric carboxymaltose improved all KCCQ domain mean scores from Week 4 onward ($P \leq 0.05$), except for self-efficacy and social limitation. Effects were present in both anaemic and non-anaemic patients.

Conclusions

HRQoL is impaired in iron-deficient patients with CHF. Intravenous FCM significantly improved HRQoL after 4 weeks, and throughout the remaining study period. The positive effects of FCM were independent of anaemia status.

Keywords

Anaemia • Chronic heart failure • Health-related quality of life • Iron deficiency

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Introduction

Patients with chronic heart failure (CHF) suffer from a marked impairment of health-related quality of life (HRQoL) compared with the normal population and patients with other chronic conditions.^{1–3} Among the factors associated with a reduced HRQoL, dyspnoea and fatigue are major symptoms of CHF that persist in many patients despite optimal drug and device management.⁴ Limited options for treatment of underlying CHF pathology have caused the focus of therapeutic attention to shift towards patient-centred outcomes such as HRQoL, particularly in those already receiving evidence-based therapy and even more so in those with limited life expectancy.^{5,6} Currently, an improvement in patient-reported outcomes is considered one of the main goals of comprehensive CHF management.^{7–9} Moreover, despite their benefits in survival, some of the usual therapies used in CHF, such as beta-blockers, have failed to prove a positive effect in terms of HRQoL.¹⁰

Iron plays a vital role in energy-dependent physiological processes such as erythropoiesis and oxidative phosphorylation,^{11,12} and iron deficiency (ID) may be a frequent and significant comorbidity in CHF.¹³ Beyond anaemia, ID is a determinant of fatigue and impaired exercise capacity in otherwise healthy populations.^{14,15} In this context, there is recent evidence that ID in CHF patients is also associated with impaired exercise capacity, worse functional New York Heart Association (NYHA) class, and poorer outcomes, although this latter observation remains controversial.^{13,16,17} Iron deficiency is, therefore, a potential treatment target to improve HRQoL in CHF patients.^{11,18}

Beyond small studies, there is little information about HRQoL in iron-deficient CHF patients and the potential benefits of iron repletion therapy. The FAIR-HF study (Ferric carboxymaltose Assessment in patients with Iron deficiency and chronic Heart Failure) was designed to determine the effects of intravenous (i.v.) ferric carboxymaltose (FCM) in iron-deficient CHF patients.¹⁸ Ferric carboxymaltose was well tolerated and significantly improved CHF symptoms, exercise capacity, and HRQoL.¹⁹ In the current study, we undertook a detailed subanalysis of FAIR-HF to gain specific insight into the effects of FCM on different domains of HRQoL in iron-deficient CHF patients.

Methods

Study design

The rationale and design of the FAIR-HF study has been previously published.¹⁸ Briefly, FAIR-HF was a randomized, double-blind, placebo-controlled, 24-week study of the effects of i.v. FCM [Ferinject®, Vifor (International), Inc., St Gallen, Switzerland] in iron-deficient patients with CHF due to systolic dysfunction, with or without anaemia. The main study inclusion criteria were NYHA class II/III, the left ventricular ejection fraction (LVEF) $\leq 40\%$ (NYHA II) or $\leq 45\%$ (NYHA III), haemoglobin (Hb) levels between 9.5 and 13.5 g/dL, and ID [defined as serum ferritin $< 100 \mu\text{g/L}$, or as serum ferritin $< 300 \mu\text{g/L}$ if transferrin saturation (TSAT) was $< 20\%$].

After 24 weeks of therapy, the patients in the FCM group experienced a significant improvement in the Patient Global Assessment (PGA) score, NYHA class (co-primary endpoints) and 6-minute walking test distance (secondary endpoint) compared with patients receiving placebo.¹⁹

Health-related quality of life measurements

Two standard instruments were used: the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) and the generic EuroQoL EQ-5D questionnaire.

The KCCQ²⁰ is a disease-specific measure of HRQoL for heart failure comprising seven domains (physical limitation, symptom stability, symptom burden, symptom frequency, self-efficacy, quality of life, and social limitation) and three summary scores [total symptom score (TSS, comprising symptom frequency and symptom burden), overall summary score (OSS, comprising physical limitation, TSS, quality of life and social limitation), and clinical summary score (CSS, comprising physical limitation, TSS)]. Scores ranged between 0 and 100, where 100 is the best possible HRQoL status. A five-unit change in the OSS was defined as the minimally noticeable clinical difference in response to treatment.²¹

The EQ-5D instrument⁹ is a generic measure of HRQoL, comprising a Visual Analogue Scale (VAS) for self-rating of general health (a score of 100 is the best possible general health status) and five domains evaluating mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In this instrument, 1 is the best possible general health status in each case; the dimensions may also be expressed as percentage of patients rating 1–3 (best to worst health status) or percentage of patients with ‘any’ complaint (scoring 2 or 3 in each domain). The results for the five domains can be converted into a single summary index score by weighting the individual values and deducting the weighted values from 1, the value for full health (i.e. state 11111). In this study, the index was multiplied by 100. The minimally important difference (MID) in the EQ-5D index score is defined as the smallest change in the index score that can be regarded as important and meaningful for health professionals, patients, and other stakeholders. Based on data from 11 patient groups in eight longitudinal studies, the MID has been estimated to be 0.074 (7.4%).^{9,22}

During the FAIR-HF study, the EQ-5D questionnaire and the KCCQ were self-administered at baseline, and at Weeks 4, 12, and 24, before any other assessment or procedure.

Statistical analysis

Data analysis was performed using the full analysis set based on the intention-to-treat principle for each assigned study group. We used a two-tailed significance level of $\alpha = 0.05$ for all assessments. We present data at baseline as mean \pm SD or number (per cent). Health-related quality of life data are presented as mean \pm SEM.

For the continuous variables, changes from the baseline value and values at Weeks 4, 12, and 24 were compared between the FCM group and the placebo group by means of repeated measures analysis of covariance. The statistical model included treatment group, visit and their interaction as categorical variables and baseline value as a continuous covariate. An unstructured covariance matrix was used.

For categorical endpoints, differences in the distribution of the two study groups were tested by means of ordered polytomous regression for repeated measures. The same explanatory variables were used as in the analyses of continuous endpoints, and an unstructured covariance matrix was used.

Missing HRQoL data at each time point were defined as the following: no EQ-5D VAS score, no EQ-5D index score, or no KCCQ OSS. Missing data for patients known to be alive and not hospitalized at the time point being analysed were imputed using the ‘last observation carried forward’ method, for which at least one previous follow-up value was required. If no preceding HRQoL values were available, the patient was excluded in that analysis. For hospitalized patients unable to complete the questionnaires, or if the patient had died

between the last time point and the planned time point, the worst reply was used for the imputation (i.e. 1 for the KCCQ individual domains, 3 for the EQ-5D sub-questions, and 0 for the EQ-5D VAS score).

Table 1 Baseline health-related quality of life

	FCM (n = 304)	Placebo (n = 155)
HRQoL: EQ-5D		
Visual analogue scale		
Missing data, n (%)	9 (3)	3 (2)
Mean \pm SEM	54 \pm 1	54 \pm 1
Index score (\times 100)		
Missing data, n (%)	6 (2)	1 (1)
Mean \pm SEM	68 \pm 1	69 \pm 1
Patients reporting any problem by domain		
Mobility, n (%)	245 (81)	131 (85)
Self-care, n (%)	146 (49)	79 (51)
Usual activity, n (%)	232 (77)	124 (81)
Pain/discomfort, n (%)	228 (76)	117 (75)
Anxiety/depression, n (%)	194 (65)	97 (63)
HRQoL: KCCQ		
Missing data, n (%)	7 (2)	4 (3)
Overall summary score, mean \pm SEM	52 \pm 1	53 \pm 1
Clinical summary score, mean \pm SEM	55 \pm 1	55 \pm 1
Total symptom score, mean \pm SEM	59 \pm 1	59 \pm 2
Physical limitation, mean \pm SEM	52 \pm 1	52 \pm 2
Symptom burden, mean \pm SEM	59 \pm 1	60 \pm 1
Symptom frequency, mean \pm SEM	59 \pm 1	58 \pm 2
Symptom stability, mean \pm SEM	54 \pm 1	53 \pm 1
Self-efficacy, mean \pm SEM	64 \pm 1	63 \pm 2
Quality of life, mean \pm SEM	47 \pm 1	48 \pm 2
Social limitation, mean \pm SEM	51 \pm 2	51 \pm 2

Visual Analogue Scale and Kansas City Cardiomyopathy Questionnaire overall summary score data were previously published, and are included here for context.¹⁶

KCCQ, Kansas City Cardiomyopathy Questionnaire.

The effects of baseline characteristics on baseline HRQoL were assessed by means of analysis of covariance models. Using simple backward elimination, non-significant variables ($P > 0.10$) were removed from the model one at a time. Tests for interaction (e.g. treatment-by-baseline NYHA) were performed by analysing the data by visit and adding the interaction term to the statistical models. All analyses were conducted with the SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA: 2000–2004).

Results

The screening and inclusion process for eligible patients, baseline characteristics, and primary and secondary endpoint results have been published.¹⁹ Here, we present otherwise unpublished specific HRQoL analyses, and only show previously published data, appropriately cited, when they are required to understand the current analyses.

The two treatment groups were well matched for patient demographic, laboratory parameters, and treatment characteristics. At the start of the study, the mean (\pm SD) age was 67.8 ± 10.3 and 67.4 ± 11.1 years in the FCM and placebo groups, respectively. In the FCM group, 52.3% of patients were women, compared with 54.8% in the placebo group.¹⁹ All patients were in either NYHA class II or III, with 83% in the FCM group and 81% in the placebo group in NYHA class III.¹⁹ The FCM and placebo groups, respectively, were well matched for mean (\pm SD) % LVEF (32.5 ± 5 and 33 ± 6) and the Hb level (11.9 ± 1.3 and 11.9 ± 1.4 g/dL).¹⁹ In both groups, 48% of patients were anaemic (Hb ≤ 12 g/dL).¹⁹

Health-related quality of life data were available for over 90 per cent of patients at all time points. The two groups had similar HRQoL scores at baseline as measured by EQ-5D VAS score, index score, and domains, and by the KCCQ summary scores and domain scores (Table 1).

Baseline health-related quality of life in chronic heart failure patients

At baseline, HRQoL was lower in patients with anaemia compared with non-anaemic patients (Table 2). Likewise, symptom severity

Table 2 Differences in baseline health-related quality of life according to anaemia status and NYHA class

	Anaemic (n = 220)	Non-anaemic (n = 221)	P (anaemic vs. non-anaemic)	NYHA III (n = 377)	NYHA II (n = 82)	P (NYHA III vs. NYHA II)
HRQoL: EQ-5D						
Visual Analogue Scale, mean \pm SEM	53.0 \pm 1.1	55.6 \pm 1.1	0.093	52.5 \pm 0.8	62.4 \pm 1.9	<0.001
Index score (\times 100), mean \pm SEM	66.2 \pm 1.0	70.7 \pm 1.1	0.002	66.7 \pm 0.8	76.5 \pm 1.6	<0.001
HRQoL: KCCQ						
Overall summary score, mean \pm SEM	49.3 \pm 1.2	55.7 \pm 1.3	<0.001	49.4 \pm 0.9	66.8 \pm 1.9	<0.001
Clinical summary score, mean \pm SEM	52.4 \pm 1.2	58.6 \pm 1.3	<0.001	52.0 \pm 0.9	71.8 \pm 1.8	<0.001
Total symptom score, mean \pm SEM	56.3 \pm 1.3	61.6 \pm 1.4	<0.005	55.5 \pm 1.0	75.2 \pm 1.9	<0.001

NYHA, New York Heart Association; EQ-5D, Euro QoL 5 Dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire.

Table 3 Absolute and percentage change from baseline in generic quality of life measured using the EQ-5D instrument

	Week 4		Week 12		Week 24	
	FCM (n = 304)	Placebo (n = 155)	FCM (n = 304)	Placebo (n = 155)	FCM (n = 304)	Placebo (n = 155)
EQ-5D Visual Analogue Scale						
Missing data, n (%)	30 (9.9)	15 (9.7)	21 (6.9)	10 (6.5)	19 (6.3)	9 (5.8)
Mean \pm SEM (% change from baseline)	6.0 \pm 0.7 (17.4 \pm 2.1)***	0.8 \pm 1.3 (4.8 \pm 2.8)	7.9 \pm 0.8 (21.4 \pm 2.3)***	2.4 \pm 1.5 (7.9 \pm 3.2)	9.1 \pm 1.0 (24.6 \pm 2.7)***	3.4 \pm 1.6 (9.9 \pm 3.3)
EQ-5D index score						
Missing data, n (%)	29 (9.5)	13 (8.4)	17 (5.6)	8 (5.2)	16 (5.3)	7 (4.5)
Mean \pm SEM, \times 100 (% change from baseline)	5.9 \pm 0.8 (12.6 \pm 1.8)***	0.6 \pm 1.5 (5.1 \pm 2.8)	6.9 \pm 1.0 (15.1 \pm 2.2)***	-1.6 \pm 1.7 (0.5 \pm 3.3)	6.6 \pm 1.2 (14.4 \pm 2.5)***	-1.0 \pm 1.8 (1.5 \pm 3.2)
Mobility, n (%) reporting improvement	46 (16.5)	15 (10.4)	55 (19.0)***	9 (6.1)	59 (20.3)**	17 (11.4)
Self-care, n (%) reporting improvement	43 (15.5)**	14 (9.8)	54 (18.8)***	17 (11.6)	61 (21.1)***	14 (9.5)
Usual activity, n (%) reporting improvement	53 (18.9)*	18 (12.7)	62 (21.4)	23 (15.6)	70 (24.1)*	23 (15.5)
Pain/discomfort, n (%) reporting improvement	57 (20.3)*	21 (14.7)	77 (26.6)***	22 (14.9)	82 (28.2)**	25 (16.8)
Anxiety/depression, n (%) reporting improvement	68 (24.3)	30 (21.0)	84 (29.1)*	33 (22.3)	94 (32.4)*	37 (24.8)

Visual Analogue Scale data were previously published, and are included here for context.¹⁶

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for ferric carboxymaltose vs. placebo.

Table 4 Absolute and percentage change from baseline in heart-failure-specific quality of life measured using the Kansas City Cardiomyopathy Questionnaire

	Week 4		Week 12		Week 24	
	FCM (n = 304)	Placebo (n = 155)	FCM (n = 304)	Placebo (n = 155)	FCM (n = 304)	Placebo (n = 155)
HRQoL: KCCQ						
Missing data, n (%)	27 (8.9)	15 (9.7)	18 (5.9)	11 (7.1)	18 (5.9)	10 (6.5)
Overall summary score, mean \pm SEM (% change from baseline)	9.4 \pm 0.9 (33.6 \pm 5.2)***	3.5 \pm 1.2 (10.6 \pm 3.3)	12.2 \pm 1.1 (41.9 \pm 5.8)***	4.6 \pm 1.4 (16.1 \pm 5.4)	12.8 \pm 1.3 (43.9 \pm 6.1)***	6.2 \pm 1.5 (21.5 \pm 6.7)
Clinical summary score, mean \pm SEM (% change from baseline)	9.3 \pm 0.9 (29.9 \pm 4.3)***	2.7 \pm 1.2 (7.0 \pm 2.5)	11.6 \pm 1.1 (36.2 \pm 4.7)***	3.3 \pm 1.4 (9.4 \pm 3.5)	11.4 \pm 1.3 (36.8 \pm 4.9)***	4.2 \pm 1.5 (12.6 \pm 3.7)
Total symptom score, mean \pm SEM (% change from baseline)	10.4 \pm 1.0 (34.1 \pm 5.1)***	3.1 \pm 1.2 (7.5 \pm 2.6)	12.7 \pm 1.2 (38.0 \pm 4.4)***	3.3 \pm 1.5 (8.2 \pm 3.3)	12.0 \pm 1.3 (36.3 \pm 4.5)***	3.9 \pm 1.6 (11.5 \pm 3.5)
Physical limitation, mean \pm SEM (% change from baseline)	8.2 \pm 1.1 (31.7 \pm 4.7)***	2.3 \pm 1.4 (9.8 \pm 3.7)	10.5 \pm 1.3 (39.5 \pm 5.9)***	3.3 \pm 1.6 (11.8 \pm 4.2)	10.7 \pm 1.5 (45.5 \pm 7.1)**	4.5 \pm 1.8 (13.5 \pm 4.1)
Symptom frequency, mean \pm SEM (% change from baseline)	10.1 \pm 1.1 (40.9 \pm 8.8)***	4.1 \pm 1.4 (12.2 \pm 3.4)	12.0 \pm 1.2 (44.2 \pm 7.9)***	3.2 \pm 1.5 (10.2 \pm 3.9)	11.5 \pm 1.4 (41.4 \pm 8.1)***	4.6 \pm 1.7 (17.6 \pm 4.6)
Symptom stability, mean \pm SEM (% change from baseline)	12.7 \pm 1.4 (32.3 \pm 3.3)***	1.6 \pm 1.9 (8.9 \pm 4.4)	14.2 \pm 1.7 (37.6 \pm 3.9)***	1.7 \pm 2.1 (11.6 \pm 5.4)	13.2 \pm 1.7 (33.8 \pm 3.7)***	4.5 \pm 2.1 (17.0 \pm 5.4)
Symptom burden, mean \pm SEM (% change from baseline)	10.8 \pm 1.1 (35.2 \pm 5.2)***	2.1 \pm 1.3 (6.1 \pm 2.7)	13.3 \pm 1.2 (40.8 \pm 5.1)***	3.3 \pm 1.6 (9.2 \pm 3.6)	12.5 \pm 1.4 (39.0 \pm 5.1)***	3.3 \pm 1.7 (10.2 \pm 3.6)
Self-efficacy, mean \pm SEM (% change from baseline)	6.9 \pm 1.3 (23.5 \pm 4.3)	5.7 \pm 1.9 (23.0 \pm 7.4)	8.9 \pm 1.3 (28.8 \pm 4.8)*	4.3 \pm 2.4 (21.3 \pm 7.4)	9.7 \pm 1.5 (30.0 \pm 5.0)	6.0 \pm 2.4 (26.3 \pm 7.8)
Quality of life, mean \pm SEM (% change from baseline)	8.7 \pm 1.1 (36.8 \pm 5.8)**	3.6 \pm 1.6 (19.8 \pm 7.1)	13.3 \pm 1.3 (54.9 \pm 7.0)***	4.5 \pm 1.6 (21.7 \pm 6.9)	14.8 \pm 1.4 (59.1 \pm 7.3)***	6.8 \pm 1.8 (31.8 \pm 8.8)
Social limitation, mean \pm SEM (% change from baseline)	10.2 \pm 1.4 (46.6 \pm 8.5)**	4.1 \pm 1.7 (15.0 \pm 5.3)	12.1 \pm 1.6 (55.2 \pm 11.0)*	7.2 \pm 2.1 (25.4 \pm 7.1)	13.1 \pm 1.7 (54.4 \pm 9.7)	8.5 \pm 2.2 (27.5 \pm 6.9)

KCCQ overall summary score data were previously published, and are included here for context.¹⁶

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for ferric carboxymaltose vs. placebo.

(NYHA class III vs. II) was associated with incrementally worse HRQoL (Table 2).

Age at baseline, gender, baseline NYHA, ischaemic aetiology of CHF, baseline serum iron, serum ferritin, TSAT, and Hb were associated with baseline QoL scores in the univariate analyses. We fitted an analysis of covariance model with a range of these possible predictors. Through backward elimination, non-significant variables were removed. In the final model, baseline NYHA class ($P < 0.001$), baseline Hb ($P = 0.02$), and baseline TSAT ($P = 0.04$) were associated with HRQoL (KCCQ OSS).

Effect of intravenous ferric carboxymaltose on health-related quality of life

As previously published, FCM significantly improved EQ-5D VAS and KCCQ OSS.¹⁹ In our analysis, we found that FCM also improved EQ-5D index scores, and other summary scores of the KCCQ, such as CSS and TSS consistently after 4 weeks of treatment initiation. These effects were maintained or increased throughout the study (FCM $P < 0.001$ vs. placebo at each time point, Tables 3 and 4). The changes from baseline in EQ-5D VAS and index scores ranged on average between 13 and 25% throughout the study, compared with $<10\%$ among the placebo group (Table 3).

There was a greater improvement in the percentage of patients reporting any complaint in each EQ-5D domain in the FCM group compared with the placebo group (Table 3). Throughout the study, significantly more ($P < 0.02$) patients reported an MID in the FCM group (37–45%) compared with the placebo group (22–29%; Figure 1). In addition to overall improvement, FCM treatment was associated with lower rates of deterioration in HRQoL reported throughout the study (Figure 2).

The proportion of patients experiencing a clinically significant five-point change in KCCQ OSS at Week 24 was significantly higher in the FCM group compared with placebo patients (61 vs. 51%; $P = 0.04$). The individual percentage changes in KCCQ CSS and TSS (Table 4) were at least three times greater among patients

receiving FCM (30–37%) than those receiving placebo (7.0–12.6%), and OSS changes were two or three times greater among the iron-treated group. Among the individual domains, the greatest differences in percentage change between FCM and placebo groups were seen in symptom-related domains, where improvements were mostly three or four times greater in the FCM group than the placebo group. Likewise, iron treatment resulted in an approximately three-fold improvement in physical limitation compared with placebo. However, there were no major differences between groups in self-efficacy scores.

As shown in Figures 3 and 4, the effects of FCM on HRQoL as measured by KCCQ were independent of a range of pre-specified variables, including baseline anaemia, renal function, age, CHF aetiology, and diabetes. The efficacy of FCM at Week 24 appeared to be affected by baseline CHF severity as indicated by NYHA class (Figure 3), an effect also observed in the KCCQ CSS ($P_{\text{Interaction}} = 0.04$), TSS ($P_{\text{Interaction}} = 0.03$), QoL score ($P_{\text{Interaction}} = 0.01$), and symptom burden score ($P_{\text{Interaction}} = 0.02$).

Although anaemia was associated with lower baseline HRQoL in patients with ID compared with ID without anaemia, there were no significant differences between FCM treatment effects observed in anaemic and non-anaemic patients at the end of the study (after adjustment for baseline differences) for the KCCQ OSS (Figure 3). Values at Week 24 in the FCM group [adjusted for baseline (\pm SEM)] in the anaemic and non-anaemic subgroups, respectively] were: EQ-5D index score 74.7 ± 1.6 vs. 75.7 ± 1.6 ($P = 0.66$); EQ-5D VAS 63.1 ± 1.3 vs. 63.8 ± 1.3 ($P = 0.74$); KCCQ OSS 66.1 ± 1.6 vs. 64.9 ± 1.6 ($P = 0.61$). The absence of differences in treatment effects according to anaemia status was also observed for other relevant domains and summary scores of the KCCQ that specifically capture information about symptoms and physical limitation such as KCCQ CSS, and about HRQoL, such as the KCCQ QoL domain (Figure 4).

Discussion

The primary analysis of the FAIR-HF study showed that FCM treatment improved overall measures of HRQoL (EQ-5D VAS and

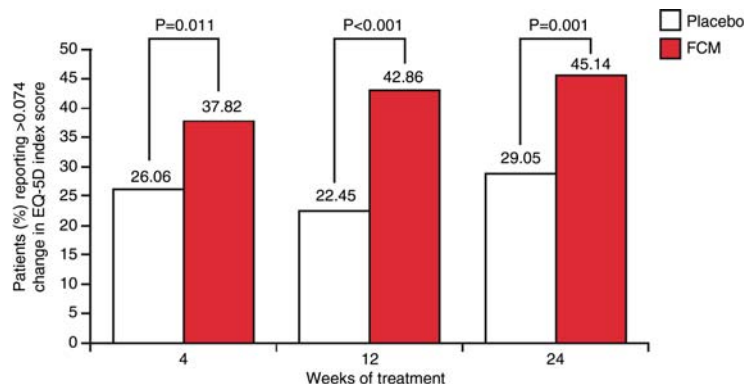
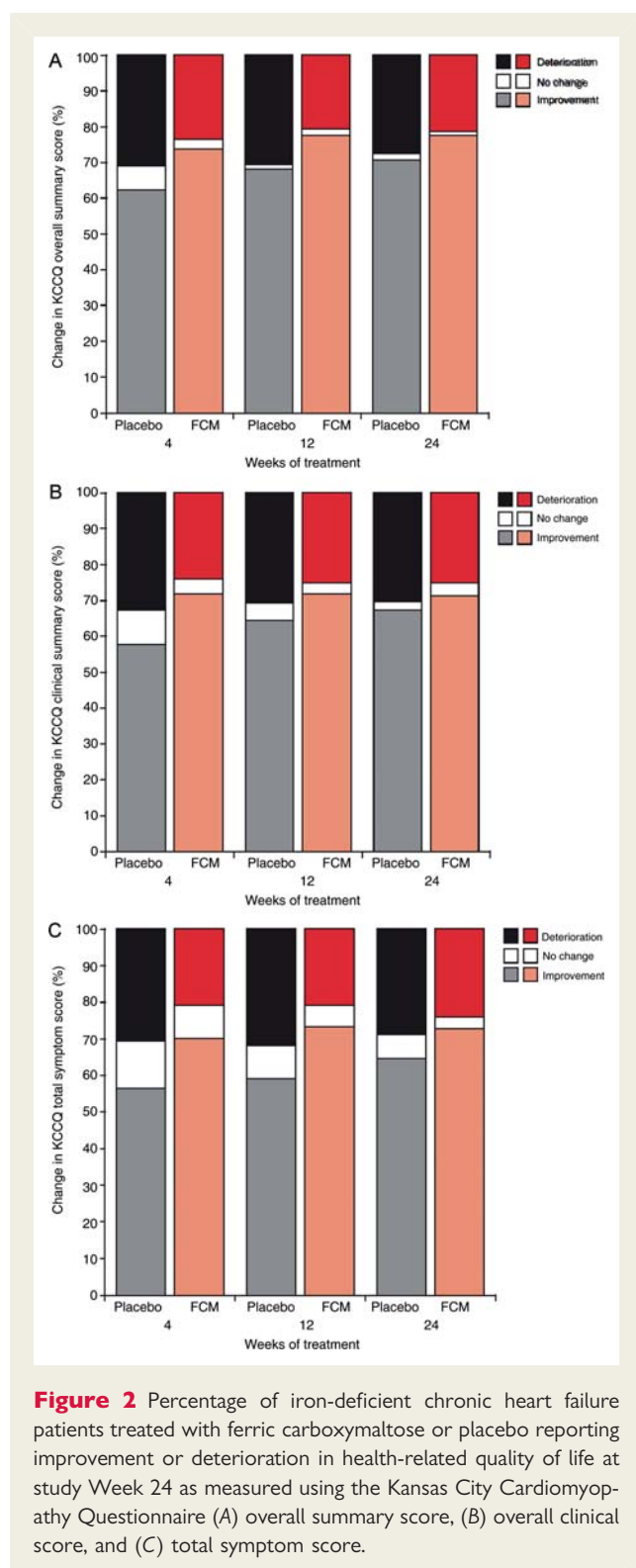


Figure 1 Percentage of iron-deficient chronic heart failure patients treated with ferric carboxymaltose or placebo reporting at least a minimally important difference in EQ-5D index score at each study time point [minimally important difference is the smallest index score change meaningful for health professionals, patients and other stakeholders, and is 0.074 (7.4%) for the EQ-5D index score].^{1,22}



index scores, and KCCQ OSS) in patients with CHF and ID after 4 weeks of treatment,¹⁹ confirming the findings of several smaller studies.^{23–25} Here, we report detailed HRQoL data for baseline status and the impact of comorbidities on the efficacy of FCM treatment.

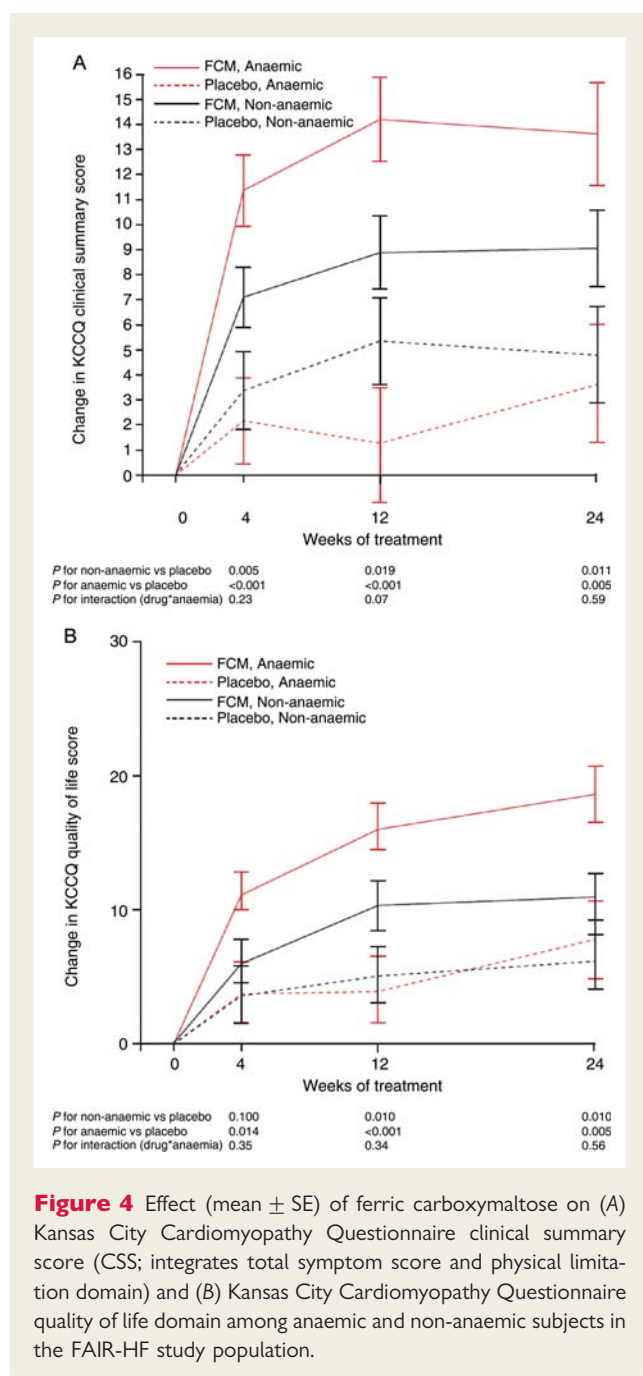
As expected for patients with CHF, cross-study comparisons revealed a markedly reduced baseline HRQoL in the FAIR-HF patients relative to age-matched normal populations.^{1,26} Health-related quality of life impairment was strongly related to domains most influenced by physical limitation, such as mobility and usual activities, although many patients also reported problems in pain/discomfort and anxiety/depression domains, highlighting the multidimensional nature of HRQoL.

The effect of FCM on HRQoL was significant throughout the study, with more patients reporting clinically meaningful changes in the FCM treatment arm. Consistent with these findings, the proportion of patients reporting any problems in the EQ-5D dimensions was significantly reduced at the end of the study only in the FCM group, and fewer patients in the FCM group experienced deteriorating HRQoL during the study, which may be important given the progressive nature of the disease.

The positive effect of FCM in HRQoL was consistent among all pre-specified subgroups, except for NYHA class. Although this latter observation may be, in part, attributable to the low sample size and the apparent improvements seen in the placebo arm among patients in NYHA class II, it may also suggest less improvement in HRQoL in patients with a lower NYHA class. New York Heart Association class II patients have better QoL than patients in higher classes² and therefore hypothetically there is less room for improvement. This interaction between NYHA class and HRQoL was observed consistently in the specific domains and the summary scores; however, there was no interaction between NYHA class and the 6MWT, an objective measure of functional capacity.¹⁹ This apparent discrepancy gives support to the evidence that the correlation between objective functional capacity and HRQoL is not perfect and that HRQoL measures may provide additional information not captured by more conventional ways of assessing physical limitation in patients with CHF.²⁷

Ferric carboxymaltose was equally effective in anaemic and non-anaemic patients and the effect was independent of baseline renal function. In the FCM group, the change was more apparent in anaemic patients, but this could mostly be accounted for by their lower baseline HRQoL.

The physiological mechanisms behind the favourable change in HRQoL due to FCM treatment have not been completely elucidated. Transferrin saturation, a marker of iron availability and probably ID at the tissue level,²⁸ was independently associated with abnormalities in HRQoL at baseline, and further work is needed to determine the relevance of this. There is some evidence that poor iron homeostasis is one of the mechanisms underlying exercise intolerance in CHF,^{13,17,19} partly due to impaired physical function as a result of ID in skeletal and myocardial muscle cells.^{14,15} In this context, recent studies have shown that patients with CHF and anaemia commonly exhibit tissue ID at the myocyte level.²⁹ Furthermore, treatment with i.v. iron may have favourable effects in cardiac structure and remodelling.³⁰ We can therefore hypothesise that ID impairs physical function and promotes symptoms such as fatigue due to impaired energy metabolism, a common feature in CHF, as well as due to abnormal erythropoiesis where anaemia is present.^{11,13,17,23} These mechanisms may explain why FCM administration significantly improved HRQoL in both anaemic



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Conflict of interest: S.D.A., P.P., J.C.C., G.F., R.W., K.D., and T.L. are members of the FAIR-HF steering committee. S.D.A. and R.W. are consultants and have received honoraria for speaking for Vifor Pharma Ltd and Amgen, Inc. S.D.A. has received honoraria for speaking for Roche Pharma and Teva. J.C.C., G.F., and T.L. have received honoraria for speaking for Vifor Pharma Ltd. P.P. is a consultant and has received honoraria for speaking for Vifor Pharma Ltd. C.M. and P.J. are employees of Vifor Pharma Ltd., Switzerland and hold stock in Galenica Ltd. M.L. received the Heart Failure Association Research Fellowship.

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